

Application No. 10/038,591
Filed: January 4, 2002
Title: ANTIBODIES TO INSULIN-LIKE GROWTH FACTOR I RECEPTOR
Confirmation No.: 1445

1-19. (Cancelled)

20. (Cancelled)

21-22. (Cancelled)

84 23. (Currently amended) A method of detecting the presence or location of an IGF-IR-expressing tumor in a subject in need thereof, comprising the steps of:

- a) administering the antibody or antigen-binding portion according to claim *34* or an antibody according to claim *39* or *46* to the subject; and
b) detecting binding of said antibody,
wherein said binding indicates the presence or location of the tumor.

85 24. (Currently amended) A method of treating cancer in a human patient wherein said patient overexpresses IGF-I or IGF-IR, comprising the step of administering to the human patient an amount of the antibody or antigen-binding portion according to claim *34* effective to treat said cancer.

86 25. (Currently amended) A method of treating a patient in need thereof, wherein said patient overexpresses IGF-I or IGF-IR, with the antibody or antigen-binding portion thereof according to claim *34*, comprising the step of administering to the patient an effective amount of the antibody.

85 *87* 26. (Currently amended) The method according to either of claims claim *24* or *25*, further comprising the step of administering an anti-neoplastic, anti-tumor, anti-angiogenic or chemotherapeutic agent.

27. (Cancelled)

28. (Cancelled)

29. (Cancelled)

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30. (Cancelled)

31. (Cancelled)

32. (Cancelled)

33. (Cancelled)

1 34. (Currently amended) A ~~human~~ monoclonal antibody that specifically binds ~~human~~ insulin-like growth factor I receptor (IGF-IR) or an antigen-binding portion of said antibody, wherein the antibody or portion comprises the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in a variable domain selected from the group consisting of:

(a) the variable domain of the light chain of antibody 2.13.2;
and

(b) the variable domain of a light chain comprising the amino acid sequence in SEQ ID NO: 6;
~~and~~

(c) the variable domain of the heavy chain of antibody 2.13.2;
(d) the variable domain of a heavy chain comprising the amino acid sequence in SEQ ID NO: 8; and
~~and~~

(e) the variable domain of a light chain comprising SEQ ID NO: 6 and the variable domain of a heavy chain comprising SEQ ID NO: 8.

2 35. (Currently amended) The ~~human~~ monoclonal antibody or antigen-binding portion according to claim 34, further comprising the amino acid sequences of the heavy chain CDRs of antibody 2.13.2 and light chain CDRs of antibody 2.13.2.

3 36. (Currently amended) A monoclonal antibody or an antigen binding portion thereof that specifically binds ~~human~~ insulin-like growth factor I receptor (IGF-IR), wherein said antibody comprises a variable domain of a ~~light~~ chain, and wherein

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said variable domain of a ~~light chain~~ comprises the amino acid sequence in SEQ ID NO: 6.

4 / 37. (Currently amended) A monoclonal antibody or an antigen-binding portion thereof that specifically binds ~~human~~ insulin like growth factor I receptor (IGF-IR), wherein said antibody comprises a ~~variable domain of a heavy chain~~, and wherein ~~said variable domain of a heavy chain~~ comprises the amino acid sequence in SEQ ID NO: 8.

5 / 38. (Currently amended) The monoclonal antibody or antigen-binding portion according to claim 37, wherein said antibody further comprises a ~~variable domain of a light chain~~, and ~~wherein said variable domain of a light chain~~ comprises the amino acid sequence in SEQ ID NO: 6.

6 / 39. (Currently amended) A monoclonal antibody that specifically binds ~~human~~ insulin-like growth factor I receptor (IGF-IR), wherein said antibody comprises the amino acid sequence of the heavy chain sequence within SEQ ID NO: 45, without the signal sequence, and the amino acid sequence of the light chain sequence within SEQ ID NO: 47, without the signal sequence.

7 / 40. (Currently amended) A monoclonal antibody or an antigen-binding portion thereof that specifically binds ~~human~~ IGF-IR, comprising ~~heavy chain CDR1, CDR2 and CDR3 regions~~, ~~said CDR regions comprising~~ the CDR1, CDR2 and CDR3 amino acid sequences, respectively, in SEQ ID NO:45.

8 / 41. (Currently amended) The monoclonal antibody or antigen-binding portion according to claim 36, ~~wherein said heavy chain~~ further comprises comprising the framework amino acid sequences in SEQ ID NO: 45.

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9 42. (Currently amended) A monoclonal antibody that specifically binds human IGF-IR comprising the amino acid sequence of SEQ ID NO: 45, without the signal sequence, or an antigen-binding portion of said antibody.

10 43. (Currently amended) A monoclonal antibody or an antigen binding portion thereof that specifically binds human IGF-IR, comprising ~~light chain CDR1, CDR2 and CDR3 regions, said CDR regions comprising~~ the CDR1, CDR2 and CDR3 amino acid sequences, respectively, in SEQ ID NO: 47.

11 44. (Currently amended) The monoclonal antibody or antigen-binding portion according to claim 43, wherein ~~said light chain further comprises~~ comprising the framework amino acid sequences in SEQ ID NO: 47.

12 45. (Currently amended) A monoclonal antibody that specifically binds human IGF-IR comprising the amino acid sequence in SEQ ID NO: 47, without the signal sequence, or an antigen-binding portion of said antibody.

13 46. (Currently amended) A monoclonal antibody that specifically binds human insulin-like growth factor I receptor (IGF-IR) wherein the heavy chain amino acid sequence is SEQ ID NO: 45, without the signal sequence, and the light chain amino acid sequence is SEQ ID NO: 47, without the signal sequence.

14 47. (Previously presented) A hybridoma cell line having American Type Culture Collection (ATCC) accession number PTA-2788.

15 48. (Currently amended) A monoclonal antibody or an antigen-binding portion thereof, that specifically binds human IGF-IR, comprising the heavy chain variable domain and the light chain variable domain of the antibody produced by the hybridoma cell line of claim 47.

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16 49. (Previously presented) The monoclonal antibody produced by the hybridoma cell line of claim *14* 47.

17 50. (Currently amended) A monoclonal antibody that specifically binds human IGF-IR comprising the heavy chain amino acid sequence and the light chain amino acid sequence of the antibody produced by the hybridoma cell line having ATCC accession number PTA-2788.

18 51. (Currently amended) A monoclonal antibody that specifically binds human IGF-IR comprising the amino acid sequence of the heavy chain and the amino acid sequence of the light chain of antibody 2.13.2.

18 *19* 52. (Previously presented) The monoclonal antibody according to claim 51, wherein the antibody is monoclonal antibody 2.13.2.

53. (Cancelled)

20 54. (Currently amended) A monoclonal antibody or antigen-binding portion thereof that specifically binds human IGF-IR, comprising a heavy chain amino acid sequence that utilizes the human V_H 3-23 gene.

55. (Cancelled)

21 56. (Currently amended) A monoclonal antibody or antigen-binding portion thereof that specifically binds human IGF-IR, comprising a light chain amino acid sequence that utilizes the human V_k A30 gene.

22 57. (Currently amended) The human monoclonal antibody or antigen-binding portion according to claim 34, wherein said antibody is selected from the group consisting of: an immunoglobulin G (IgG), an IgM, an IgE, an IgA or an IgD molecule, a single chain antibody or a bispecific antibody.

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13 58. (Previously presented) The antigen-binding portion according to claim *34*, wherein said portion is selected from the group consisting of: a Fab fragment, an $F(ab')_2$ fragment and an Fv fragment.

24 59. (Previously presented) The antigen-binding portion according to claim *35*, wherein said portion is selected from the group consisting of: a Fab fragment, an $F(ab')_2$ fragment and an Fv fragment.

3 60. (Previously presented) The antigen-binding portion according to claim *36*, wherein said portion is selected from the group consisting of: a Fab fragment, an $F(ab')_2$ fragment and an Fv fragment.

4 61. (Previously presented) The antigen-binding portion according to claim *37*, wherein said portion is selected from the group consisting of: a Fab fragment, an $F(ab')_2$ fragment and an Fv fragment.

5 62. (Previously presented) The antigen-binding portion according to claim *38*, wherein said portion is selected from the group consisting of: a Fab fragment, an $F(ab')_2$ fragment and an Fv fragment.

7 63. (Previously presented) The antigen-binding portion according to claim *40*, wherein said portion is selected from the group consisting of: a Fab fragment, an $F(ab')_2$ fragment and an Fv fragment.

8 64. (Previously presented) The antigen-binding portion according to claim *41*, wherein said portion is selected from the group consisting of: a Fab fragment, an $F(ab')_2$ fragment and an Fv fragment.

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9 30 65. (Previously presented) The antigen-binding portion according to claim 42, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

10 31 66. (Previously presented) The antigen-binding portion according to claim 43, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

11 32 67. (Previously presented) The antigen-binding portion according to claim 44, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

12 33 68. (Previously presented) The antigen-binding portion according to claim 45, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

15 34 69. (Previously presented) The antigen-binding portion according to claim 46, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

20 35 70. (Previously presented) The antigen-binding portion according to claim 47, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

21 36 71. (Previously presented) The antigen-binding portion according to claim 48, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

22 37 72. (Previously presented) The antigen-binding portion according to claim 49, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

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38/73. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 34 and a pharmaceutically acceptable carrier.

39/74. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 35 and a pharmaceutically acceptable carrier.

40/75. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 36 and a pharmaceutically acceptable carrier.

41/76. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 37 and a pharmaceutically acceptable carrier.

42/77. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 38 and a pharmaceutically acceptable carrier.

43/78. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 39 and a pharmaceutically acceptable carrier.

44/79. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 41 and a pharmaceutically acceptable carrier.

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4580. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 42 and a pharmaceutically acceptable carrier.

4681. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 43 and a pharmaceutically acceptable carrier.

4782. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 44 and a pharmaceutically acceptable carrier.

4883. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 45 and a pharmaceutically acceptable carrier.

4984. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 48 and a pharmaceutically acceptable carrier.

5085. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 54 and a pharmaceutically acceptable carrier.

5186. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 56 and a pharmaceutically acceptable carrier.

5287. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 57 and a pharmaceutically acceptable carrier.

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53 98. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody according to claim 39 and a pharmaceutically acceptable carrier.

54 99. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody according to claim 46 and a pharmaceutically acceptable carrier.

55 90. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody according to claim 49 and a pharmaceutically acceptable carrier.

56 91. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody according to claim 50 and a pharmaceutically acceptable carrier.

57 92. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody according to claim 51 and a pharmaceutically acceptable carrier.

58 93. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody according to claim 52 and a pharmaceutically acceptable carrier.

94. (Cancelled)

59 95. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody according to claim 54 and a pharmaceutically acceptable carrier.

96. (Cancelled)

60 97. (Previously presented) The pharmaceutical composition according to claim 73, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

61 98. (Previously presented) The pharmaceutical composition according to claim 74, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

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62 99. (Previously presented) The pharmaceutical composition according to claim *75*, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

41 63 100. (Previously presented) The pharmaceutical composition according to claim *76*, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

42 64 101. (Previously presented) The pharmaceutical composition according to claim *77*, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

43 65 102. (Previously presented) The pharmaceutical composition according to claim *78*, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

44 66 103. (Previously presented) The pharmaceutical composition according to claim *79*, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

45 67 104. (Previously presented) The pharmaceutical composition according to claim *80*, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

46 68 105. (Previously presented) The pharmaceutical composition according to claim *81*, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

69 69 106. (Previously presented) The pharmaceutical composition according to claim *82*, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

70 70 107. (Previously presented) The pharmaceutical composition according to claim *83*, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

71 71 108. (Previously presented) The pharmaceutical composition according to claim *84*, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

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72 109. (Previously presented) The pharmaceutical composition according to claim 85, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

73 110. (Previously presented) The pharmaceutical composition according to claim 86, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

74 111. (Previously presented) The pharmaceutical composition according to claim 87, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

75 112. (Previously presented) The pharmaceutical composition according to claim 88, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

76 113. (Previously presented) The pharmaceutical composition according to claim 89, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

77 114. (Previously presented) The pharmaceutical composition according to claim 90, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

78 115. (Previously presented) The pharmaceutical composition according to claim 91, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

79 116. (Previously presented) The pharmaceutical composition according to claim 92, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

80 117. (Previously presented) The pharmaceutical composition according to claim 93, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

118. (Cancelled)

81 119. (Previously presented) The pharmaceutical composition according to claim 95, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

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80 120. (Previously presented) An isolated cell line that produces the antibody according to claim 74.

81 121. (Previously presented) The cell line according to claim 120 that produces antibody 2.13.2, or an antibody comprising the amino acid sequences of antibody 2.13.2.

82 122. (Currently amended) A method for decreasing IGF-IR activation in a subject in need thereof comprising the step of administering to the subject an anti-IGF-IR antibody or antigen-binding portion according to claim 3934.

83 123. (Currently amended) A method for increasing IGF-IR associated tyrosine phosphorylation in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody or antigen-binding portion according to claim 3934.

90 124. (Currently amended) A method for decreasing IGF-IR signaling in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody or antigen-binding portion according to claim 3934.

91 125. (Currently amended) A method for decreasing IGF-IR binding to IGF-I or IGF-II in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody or antigen-binding portion according to claim 3934.

92 126. (Currently amended) A method for decreasing the level of IGF-IR in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody or antigen-binding portion according to claim 3934.

93 127. (Currently amended) A method for inhibiting tumor growth in a subject in need thereof wherein said subject overexpresses IGF-I or IGF-IR, comprising

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the step of administering to the subject an anti-IGF-IR antibody or antigen-binding portion according to claim ⁶39³⁴.

⁹³
94 128. (Previously presented) The method according to claim ¹27, wherein the tumor is a colorectal tumor.

⁹³
95 129. (Previously presented) The method according to claim ¹27, wherein the tumor is a breast cancer tumor.

⁹³
96 130. (Previously presented) The method according to claim ¹27, wherein the tumor is an epidermoid carcinoma cell tumor.

⁹³
97 131. (Previously presented) The method according to claim ¹26, wherein the anti-neoplastic agent is adriamycin.

⁹⁸
13 132. (Currently amended) A method of detecting the presence or location of an IGF-IR-expressing tumor in a subject in need thereof, comprising the steps of: ⁶

(a) administering the antibody according to any one of claims ³⁹
or 46 or 51; and

(b) detecting binding of said antibody, determining the expression of IGF-IR in the subject by localizing where the antibody has bound; and

(c) diagnosing the presence or location of the tumor wherein said binding indicates the presence or [a] location of the tumor.

⁹⁹
13 133. (Currently amended) A method of treating cancer in a human patient wherein said patient overexpresses IGF-I or IGF-IR, comprising the step of administering to the human patient an amount of the antibody according to claim ⁶39 or ¹³46 effective to treat said cancer.

¹⁰⁰
13 134. (Currently amended) A method of treating a patient in need thereof with the antibody according to claim ³⁹or 46 or 51, wherein said patient overexpresses

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IGF-I or IGF-IR, comprising the step of administering to the patient an effective amount of the antibody.

~~100~~ 101 135. (Currently amended) The method according to either of claims ~~133~~ ⁹⁹ or ~~134~~, further comprising the step of administering an anti-neoplastic, anti-tumor, anti-angiogenic or chemotherapeutic agent.

~~102~~ 136. (Previously presented) A method for decreasing IGF-IR activation in a subject in need thereof comprising the step of administering to the subject an anti-IGF-IR antibody according to claim ~~39~~ or ~~46~~.

~~103~~ 137. (Previously presented) A method for increasing IGF-IR associated tyrosine phosphorylation in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody according to claim ~~39~~ or ~~46~~.

~~104~~ 138. (Previously presented) A method for decreasing IGF-IR signaling in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody according to claim ~~39~~ or ~~46~~.

~~105~~ 139. (Previously presented) A method for decreasing IGF-IR binding to IGF-I or IGF-II in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody according to claim ~~39~~ or ~~46~~.

~~106~~ 140. (Previously presented) A method for decreasing the level of IGF-IR in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody according to claim ~~39~~ or ~~46~~.

~~107~~ 141. (Currently amended) A method for inhibiting tumor growth in a subject in need thereof wherein said subject overexpresses IGF-I or IGF-IR, comprising the step of administering to the subject an anti-IGF-IR antibody according to claim ~~39~~ or ~~46~~.

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108 142. (Previously presented) The method according to claim 141, wherein the tumor is a colorectal tumor.

109 143. (Previously presented) The method according to claim 141, wherein the tumor is a breast cancer tumor.

110 144. (Previously presented) The method according to claim 141, wherein the tumor is an epidermoid carcinoma cell tumor.

111 145. (Previously presented) The method according to claim 135, wherein the anti-neoplastic agent is adriamycin.

146. (Cancelled)

147. (Cancelled)

148. (Cancelled)

149. (Cancelled)

150. (Cancelled)

112 151. (New) A monoclonal antibody that specifically binds insulin-like growth factor I receptor (IGF-IR) or an antigen-binding portion of said antibody, wherein the antibody or portion comprises the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in a heavy chain variable domain selected from the group consisting of:

(a) the variable domain of the heavy chain of antibody 2.13.2;
and

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(b) the variable domain of a heavy chain comprising the amino acid sequence in SEQ ID NO: 8.

132. (New) The monoclonal antibody or antigen-binding portion according to claim 151, wherein said antibody is selected from the group consisting of: an immunoglobulin G (IgG), an IgM, an IgE, an IgA or an IgD molecule, a single chain antibody or a bispecific antibody.

14123. (New) The antigen-binding portion according to claim 151, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

1514. (New) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 151 and a pharmaceutically acceptable carrier.

1615. (New) The pharmaceutical composition according to claim 151, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

1716. (New) An isolated cell line that produces the antibody according to claim 151.

1817. (New) The monoclonal antibody or antigen-binding portion thereof according to claim 154, wherein the heavy chain amino acid sequence further utilizes a human D6-19 gene and a human JH6 gene.

1918. (New) The monoclonal antibody or antigen-binding portion according to claim 156, wherein the light chain amino acid sequence further utilizes a human Jκ1 gene.

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120 159. (New) A method of detecting the presence or location of an IGF-IR expressing tumor in a subject, comprising the steps of:

a) administering the antibody according to claim 16 to the subject; and

b) detecting binding of said antibody, wherein said binding indicates the presence or location of the tumor.

121 160. (New) A monoclonal antibody that specifically binds insulin-like growth factor I receptor (IGF-IR) or an antigen-binding portion of said antibody, wherein the antibody or portion comprises the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the variable domain of a light chain comprising SEQ ID NO: 6 and the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the variable domain of a heavy chain comprising SEQ ID NO: 8.

122 161. (New) The monoclonal antibody or antigen-binding portion according to claim 160, wherein said antibody is selected from the group consisting of: an immunoglobulin G (IgG), an IgM, an IgE, an IgA or an IgD molecule, a single chain antibody or a bispecific antibody.

123 162. (New) The antigen-binding portion according to claim 160, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

124 163. (New) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 160 and a pharmaceutically acceptable carrier.

125 164. (New) The pharmaceutical composition according to claim 160, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

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126 165. (New) An isolated cell line that produces the antibody according to
claim 160.

127 166. (New) The method according to claim 24, further comprising the
step of administering at least one additional chemotherapeutic agent.

128 167. (New) The method according to claim 24, wherein said method
further comprises radiotherapy.

129 168. (New) The method according to claim 163, further comprising the
step of administering at least one additional chemotherapeutic agent.

130 169. (New) The method according to claim 133, wherein said method
further comprises radiotherapy.